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10/540,577	12/16/2005	Tetsuro Kikuchi	Q86357	6428

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
10/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,577	KIKUCHI ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37,38,40,41,43-45,54-56 and 58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 37-38, 40-41, 43-45, 54-56 and 58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/27/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 37-38, 40-41, 43-45, 54-56 and 58-62 are pending

Amended claims set submitted on 08/17/2010 is acknowledged where claim 1 and 54 were amended. Claims under consideration in the instant action are claims 1, 37-38, 40-41, 43-45, 54-56 and 58-62.

Applicants' arguments, filed 08/17/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

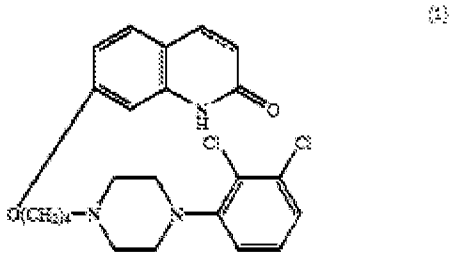
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of claims 1, 37-38, 41, 43-45, 54-56 and 59-62 under 35 U.S.C. 103(a) as being unpatentable over Wong et al. et al(US 2002/0156067, already of record) and Jordan et al. (US 2002/0173513) further in view of Harvey et al (reference already of record) as evidenced by Owens et al (reference already of record) are maintained for reasons of record restated below.

Claims 1 and 54 were amended to delete the term " compound selected from" to overcome the 112 2nd rejection set forth in the previous office action and claim 44 was amended to rectify a spelling error as such did not change the subject matter considered in the rejection below. As such the newly amended claims are appropriately rejected in the rejection below.

Original rejection:

Jordan et al. teaches a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype [0035]. Jordan et al. teaches carbostyril derivatives represented by the following formula (1) where the carbon-carbon atom between 3 and 4-positions in the carbostyril skeleton is single or a double bond.



Jordan et al. teaches his inventive compounds to be a potent, partial $5HT_{1A}$ receptor agonist and as being useful in the treatment of various disorders of the central nervous system associated with the 5-HT_{1A} receptor which includes various forms of **depression such as endogenous depression, major depression, melancholia and treatment resistant depression** etc. ([0042], reference claims 1 and 21-22). Jordan et al. teaches the method of treatment wherein the inventive carbostyril compound is **aripiprazole,** which is the compound of formula 1 above where the carbon-carbon atom between 3-4 position is a single bond (reference claim 20) and further teaches that compounds of his invention can be suitably **prepared into pharmaceutically acceptable formulations** [0043]..As such an ordinarily skilled artisan would be motivated to utilize aripiprazole in the treatment of mood disorders specifically depression from the teachings of Jordan et al.

Jordan et al. however does not teach the composition or methods to treat depression comprising a combination of aripiprazole in combination with a serotonin reuptake inhibitor such as citalopram

However, Wong et al. expressly teaches pharmaceutical composition and methods of their use comprising a) one or more norepinephrine reuptake inhibitors and b) one or more neuroleptic agents (Reference claim 1). Wong et al. describes his inventive composition to provide relief from several nervous system disorders with reduced side effects [0003] Wong et al. teaches among the compounds listed for component a)norepinephrine reuptake inhibitors **are duloxetine, venlafaxine, and milnacipran** (Reference claim 2). Among the compounds listed by Wong et al. as neuroleptic agents, component b**) is aripiprazole** (Reference claim 5). Example 2 describes the preparation of the composition, in that the active components are combined in a **pharmaceutically acceptable carrier** [0047]. Wong et al. discloses that the composition of his invention is used to treat any of the diseases or disorders of the central nervous system. Representative diseases or disorders include, but are not limited to the following: **depression, schizophrenia, neurodegenerative disorders**, migraine headaches, cluster headaches, an age-associated learning and mental disorder, bipolar disorder, a movement disorder (e.g., Tourette's syndrome)etc. ([0042] and claims 1,2,5,9 and 19). Wong et al. teaches that both commonly used typical and atypical neuroleptic agents can cause number of neurological side effects [0013-0014]. Wong et al. also teaches the need for pharmaceutical compositions that would have both the therapeutic benefits of the neuroleptic agents (typical or atypical) but with

reduced side effects [0013]. **Furthermore Wong et al. teaches that the combination of the norepinephrine reuptake inhibitor with a neuroleptic provides rapid relief to those suffering from disorders of the central nervous system with a minimal amount of deleterious side effects**, more typically that the incidence of weight gain typically associated with the administration of atypical neuroleptic agents in minimized by the administration of the norepinephrine reuptake inhibitors. [0044].

With references to the specific serotonin reuptake inhibitors citalopram and escitalopram claimed in the instant application, these two drugs elicit anti-depressant effect by inhibiting serotonin reuptake. Although Wong et al. is silent as to these specific drugs, Wong et al. cites drugs such as venlafaxine, which also inhibits serotonin reuptake as evidenced by Harvey et al (Arch Gen Psychiatry/ vol 57, May 2000, page 503-509). Harvey teaches that v**enlafaxine is an antidepressant with a mechanism of action that is believed to involve inhibition of the uptake pumps for serotonin and norepinephrine** (page 503, left col. 1st paragraph) and concludes that the in-vivo evidence in healthy humans suggests that both serotonin (5-HT) and norepinephrine uptake inhibitions are mechanisms of action of venlafaxine. Citalopram and escitalopram are also serotonin reuptake inhibitors as evidenced by Owens (CNS Spectr, abstract, 2002 Apr/ 7 (4) page 34-9). Owens teaches that **citalopram is one of a selective serotonin reuptake inhibitor and it's S-enantiomer also known as escitalopram is one of the most selective serotonin reuptake inhibitor available**. As such venlafaxine taught by Wong et al. is a functional equivalent of citalopram and escitalopram and thus substitution of the antidepressants taught by Wong et al. with

other similarly functioning drugs such as citalopram or escitalopram would have been obvious to one of ordinary skill in the art at the time of invention. Substituting equivalents, namely serotonin reuptake inhibitors, motivated by the reasonable expectation that the respective species will behave in a comparable manner or even provide comparable results in related circumstances, see *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) is prima facie obvious. Moreover, the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious, see *In re Font* 213 USPQ 532. Due to the fact that Harvey et al. teaches venlafaxine as a serotonin reuptake inhibitor and Owens teaches citalopram and escitalopram as also serotonin reuptake inhibitor both useful for the treatment of depression and Wong et al teaches the combination of atypical antipsychotic drug such as aripiprazole with serotonin reuptake inhibitor such as Venlafaxine, the references provide the skilled artisan with the necessary motivation to use citalopram or escitalopram in combination with a atypical antipsychotic such as aripiprazole in the composition of Wong et al. for the treatment of mood disorders.

In view of the foregoing references, the instantly claimed pharmaceutical composition would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Jordan et al. explicitly teaches aripiprazole as being an effective drug in the treatment of mood disorders such as depression. Wong et al. et al. teaches pharmaceutical composition comprising of (a) one or more norepinephrine reuptake inhibitors such as venlafaxine and (b) one or more neuroleptic agents such as aripiprazole. Harvey and Owens teach that Citalopram an escitalopram are functional

equivalents of venlafaxine. Accordingly all of the materials instantly claimed were known in the art to be used for treatment of the disorders of the central nervous system more specifically depression. The prior art also teaches solution to the problem of decreasing adverse effects experienced with treatment of neuroleptics alone by combining with a serotonin reuptake inhibitors. This solutions to the prior art problem which is the combination of the neuroleptics with norepinephrine reuptake inhibitors also provides the skilled artisan motivation to combine the references. Moreover, both aripiprazole and serotonin reuptake inhibitors such as citalopram/escitalopram are individually known in the art as agents to combat depression, whose efficacy when administered alone is well established for the treatment of depression. First, It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself. The natural presumption that two individually known antidepressant would, when combined, provide a third composition also useful for treating depression flows logically from each having been individually taught in the prior art. In addition, *In re Diamond and Kellman*, 149 USPQ 562 (C.C.P.A. 1966), supports the obviousness of combining two drugs known to be useful for the same purpose. In *Diamond*, Appellants were claiming a combination of adenosine-5-monophosphate

(A5MP) and a glucocorticoid. The Examiner cited prior art teaching that A5MP and glucocorticoids were known in the art to be useful for treating collagen diseases and that combining drugs for the treatment of disease is suggested by the prior art. Appellants argued that the combination of the two drugs is non-obvious since there is no teaching to combine these two out of all known anti-inflammatory agents. The Court was not persuaded by this argument, stating that:

> "...we think it clear that it is a standard practice in this art to combine ingredients."
> "We are not convinced of non-obviousness of the combination of the two drugs, A5MP and a glucocorticoid such as hydrocortisone, for use as an anti-inflammatory composition, particularly since the record supports the solicitor's contention that the drugs selected are two of the commonly used drugs in the treatment of such collagen diseases."

Finally, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

The Examiner would like to draw Applicant's attention to the following: "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". *KSR v. Teleflex*, 127 S,Ct. 1727, 1740 (2007) (quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the

relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (*id.*). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR v. Teleflex*, 127 S.Ct. 1727, 1741 (2007).

The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." *id* at 1742. Consistent with this reasoning, it would have been obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive at compositions "yielding no more than one would expect from such an arrangement". In this instance since the prior art teaches additive or synergistic effects of the combination of atypical antipsychotic agent such as aripiprazole in combination with serotonin reuptake inhibitors as they provide better treatment options for disorders of the central nervous system such as depression with lower side effects, it would have been obvious to one of ordinary skill in the art to combine aripiprazole with a serotonin reuptake inhibitor such as Citalopram or escitalopram One skilled in the art would have been imbued with at least a reasonable expectation that a combination of aripiprazole and escitalopram or citalopram would yield promising results in terms of treating depression resulting in the decrease of deleterious effects associated with neuroleptic treatment alone.

Response to applicant's arguments submitted on 08/17/2010

Applicant traverses the above rejection with the following arguments:

a. Applicant's disagree and submit that citalopram and escitalopram are not functional equivalent of venlafaxine, since venlafaxine acts both on serotonin and norepinephrine and has been reported as having superior effects when compared to selective reuptake inhibitor such as citalopram or escitalopram. Applicants have submitted three journal articles to support their position and argue that one of ordinary skill in the art would not consider venlafaxine as a functional equivalent to citalopram or escitalopram and would therefore not arrive at the claimed invention.

b. Wong et al. does not teach or suggest regarding the effects of the concomitant use of aripiprazole with duloxetine, venlafaxine or milnacipram and thus requiring a comparison of the claimed invention to this combination of aripiprazole with duloxetine, venlafaxine or milnacipram is based on improper hindsight.

c. Wong et al. does not demonstrate the shortening of the prolonged immobility time in the forced swimming test of mice as is the case with the instantly claimed combination.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

First, it should be noted that the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. Applicant is further reminded that the obviousness rejection is not an anticipation rejection. The above mentioned references clearly teach a combination of aripiprazole and citalopram for treatment of depression. In obviousness rejection a combination of references is used, and the references are relied upon in combination

and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references that make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the combination of the cited references. *In re Young*, 403 F.2d 754, 159 USPQ 725(CCPA 1968); *In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).* Moreover, it is noted that rejections under 35 U.S.C. 103(a) are based on combinations of references, where the secondary references are cited to reconcile the deficiencies of the primary reference with the knowledge generally available to one ordinary skill in the art to show that the differences between Applicant's invention and the prior art are such that they would have been modifications that were *prima facie* obvious to the skilled artisan. It is noted that the claimed invention is not required to be expressly suggested in its entirety by any one or all of the references cited under 35 U.S.C. 103(a). Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In response to applicant's argument that Venlafaxine and citalopram are not functional equivalents, Examiner, finds this argument unpersuasive. While venlafaxine being a SNRI (serotonin norepinephrine reuptake inhibitor) might have an additional function which is the inhibition of norepinephrine reuptake, it clearly has the function of inhibition of serotonin reuptake which is the functional properties of Citalopram and escitalopram which are SSRI (selective serotonin reuptake inhibitors). As such with respect to inhibition of serotonin reuptake both venlafaxine and citalopram are functional

inhibitors. Besides both are known in the art as being useful in the treatment of depression and as such are functional equivalent with respect to their therapeutic activity.

With respect to the references supplied by the applicant in support of their argument examiner would like to point out the following:

1. Smith et al. (British Journal of Psychiatry, 20002): (a) This reference does not compare the effects of venlafaxine to citalopram or escitalopram as instantly claimed, The SSRI's used in the study was Fluoxetine, Fluvoxamine, paroxetine and sertraline (b) While the report teaches that Venlafaxine has greater efficacy as anti-depressant than SSRI, it does not teach that SSRI's does not have any anti-depressant effect. (c) Smith et al. recite that at lower doses, venlafaxine appears to act as an SSRI and it is unclear as to at what dose significant noradrenaline effect occur (page 402). (d) and finally Smith et al recites that the size of the patients used in their meta-analysis is small against other clinical areas and suggests that further randomized trials are required to find out how generalizable this result is to different settings and whether venlafaxine has increased effectiveness. Accordingly, Smith et al. does not provide convincing evidence that venlafaxine and citalopram are functionally different.

2. Thase et al. (British Journal of Psychiatry, 2001) : (a) the reference does not compare the effect of venlafaxine with citalopram or escitalopram as instantly claimed. The SSRI's used in the study was Fluoxetine and Fluvoxamine, paroxetine and sertraline. (b) This study looks at the effect on the remission rates during treatment of depression with SSRI's or venlafaxine, while the study results showed that venlafaxine

had remission rates of 45% which is greater than that of SSRI (35%), it is noted that the difference between placebo and SSRIs was also significant (page 236, right col.) compared to placebo (25%) (c) Other studies have shown that there was no evidence of remission or response rates which compared the minimum therapeutic doses of venlafaxine, with fluoxetine and paroxetine and that there are non-significant (not statistically significant) differences between venlafaxine and fluoxetine and inconsistent findings (page 239). Accordingly, Thase et al. does not provide convincing evidence that venlafaxine and citalopram are functionally different.

3. Stahl et al. (Biological Psychiatry 2002) : (a) the reference does not compare the effect of venlafaxine with citalopram or escitalopram as instantly claimed. The SSRI's used in the study was Fluoxetine, Paroxetine and Fluvoxamine. (b) while Venlafaxine showed better results than SSRI's it is noted that SSRI's also had a statistically significant advantage over placebo and in week 3 there was no statistically significance between the results of venlafaxine and fluoxetine (page 1170). (c) Stahl et al. disclose that it is unclear weather SSRIs may exhibit comparable efficacy to venlafaxine when treatment exceeds 8 weeks (page 1172). Accordingly, Stahl et al. does not provide convincing evidence that venlafaxine and citalopram are functionally different

. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was

within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this regard, the cited prior art teaches combinations of Aripiprazole with serotonin receptor uptake inhibitors, prior art also teaches that the two drugs used in the instant invention are well known for their anti-depressant effect. Combination therapy is also well established and routine in the art of psychiatric disorders as evidenced by the cited prior art. As such, there is nothing unobvious about taking two known anti-depressant agents and combining them to treat depression. Applicant's disclosure is not needed to provide any motivation in this regard because clinicians have been combining anti-depressant agents in treatment of depression previously.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., does not demonstrate the shortening of the prolonged immobility time in the forced swimming test of mice) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants argue that the previously submitted Rule 132 declaration provides unexpectedly superior results. Applicants state that in their test paradigm what was intended in the test was to qualitatively investigate whether the pharmacological functions of the two drugs can exert a synergistic anti-depression effect and the test established that when the two drugs exist in the animal body they show an anti-

depressant effect by the interactions thereof, so that a skilled artisan would understand that the two drugs can exert an anti-depression effect only if the pharmacological functions of each of the drugs are qualitatively co-used i.e., the two drugs have a synergistic effect.

Applicant's results have been carefully considered but the Examiner is not persuaded that an "unexpected result" has been demonstrated. As discussed above, aripiprazole has shown additive or *synergistic effects* in the treatment disorders of central nervous systems such as depression when combined with serotonin reuptake inhibitors. (Wong et al). As such, it is not unexpected that aripiprazole also shows a synergistic effect when combined with citalopram or escitalopram. Applicants have presented no evidence that the combination of aripiprazole and citalopram/escitalopram is unexpectedly superior to combinations of aripiprazole with *other* serotonin reuptake inhibitors. In fact, Applicant's results appear to show that aripiprazole demonstrates a synergistic effect when combined with duloxetine, venlafaxine, milnacipram, escitalopram, paroxetine or sertraline (page 6 , 1st paragraph of the submitted 132 declaration dated 03/18/2009).

Applicants are reminded that a "synergistic" effect is not per se unexpected. Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck& Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a *prima facie* case

of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

In this case, where the prior art suggests and motivates the treatment of depression comprising administration of a combination of aripiprazole with serotonin reuptake inhibitors, it is obvious to combine aripiprazole with other known serotonin reuptake inhibitors for the treatment of depression. One skilled in the art would reasonably expect that aripiprazole combined with serotonin reuptake inhibitors such as citalopram or escitalopram would provide synergistic effect in the treatment of depression. Given the known efficacy of both aripiprazole and serotonin reuptake inhibitors such as citalopram/escitalopram in the treatment of depression when administered alone or in combination with other antidepressants, the skilled artisan would expect that the combination of aripiprazole with citalopram/escitalopram would also be effective in the treatment of depression. Furthermore, in view of the fact that aripiprazole has been shown to be additive or synergistic when combined with other serotonin reuptake inhibitors, the skilled artisan would not find it "unexpected" that aripiprazole combined with citalopram/escitalopram is also synergistic.

Accordingly, the arguments set forth by the applicant are unpersuasive and the rejection is maintained.

Claim 40 and 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al., Wong et al. and Harvey as evidenced by Owens et al as applied to claims 1, 37-39, 41, 43-45, 54-56 and 59-62 above, and further in view of Bando et al (US 2004/0058935, PCT filing date of Sept 25, 2002)

Jordan et al., Wong et al. and Harvey teach as discussed supra and are applied here in the same manner. The cited references do not teach the composition or the method wherein the aripiprazole is anhydrous aripiprazole crystals B.

However, Bando et al teaches low hygroscopic forms of aripiprazole and processes for their preparations thereof which will not convert to a hydrate or lose their original solubility even when a medicinal preparation containing the aripiprazole anhydride crystals is stored for an extended period. (Abstract). Bando et al teaches the disadvantages of using hydrous forms of aripiprazole, (i) the hydrous forms of aripiprazole have the disadvantage of being less bioavailable and less dissoluble than the anhydrous forms of aripiprazole (ii)the variation in the amount of hydrous versus anhydrous aripiprazole drug substance from batch to batch could fail to meet specifications set by drug regulatory agencies. (iii) The milling may cause the drug substance, conventional anhydride, to adhere to manufacturing equipment which may further result in processing delay, increased operator involvement, increased cost, increased maintenance and lower production yield.(iv) the potential for absorbance of moisture during storage and handling would adversely affect the dissolubility of aripiprazole drug substance. Thus shelf-life of the product could be significantly decreased and/or packaging costs could be significantly increased [0006]. Bando et al

teaches a reduced hygroscopic form of aripiprazole which is a crystalline substance defined as Anhydride B which is more amenable to pharmaceutical processing and formulation [0009] According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance is aripiprazole Anhydride Crystals B and will not substantially convert to a hydrous form of aripiprazole when properly stored even for an extended period. For instance, said aripiprazole anhydride crystals B can be stored under a relative humidity (RH) of 60% and at a temperature of 25.degree. C., even for a period not less than 4 year [0083]

Therefore, it would have been obvious to one of ordinary skilled in the art to combine the teachings of the cited references above and use aripiprazole B in the compositions and methods taught be Jordan et al, Wang and Harvey and Winnans. An ordinarily skilled artisan would be motivated from Bando et al's teachings of the disadvantages of the hydrous aripiprazole and the advantages of using anhydrous crystals of aripiprazole B which in medicinal compositions which is increase in stability and decrease in costs. Bando et al's teachings provide an artisan a reasonable expectation of success that using aripiprazole B in place of other aripiprazole in a composition would enhance its stability and ultimately reduce costs.

Response to applicant's arguments filed on 08/17/2010:

Please refer to the response to arguments after the previous rejection for the examiners reply to applicant's arguments.

Conclusion

Claims 1, 37-38, 40-41, 43-45, 54-56 and 58-62 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614